

Claims

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1. A vaccine comprising a pharmaceutically acceptable carrier or diluent and a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of extracytoplasmic proteins.

2. A vaccine according to claim 1 wherein the protein encoded by the mutant gene is a periplasmic protein.

10 3. A vaccine according to claim 1 or 2 wherein the protein encoded by the mutant gene promotes the folding of secreted proteins.

4. A vaccine according to claim 1, 2 or 3 wherein the protein encoded by the mutant gene is a peptidyl-prolyl cis-trans isomerase (PPiase).

15 5. A vaccine according to claim 4 wherein the PPiase is a member of the parvulin family of PPiases.

6. A vaccine according to any one of the preceding claims wherein the protein encoded by the mutant gene is SurA.

20 7. A vaccine according to any one of the preceding claims wherein the bacterium is further attenuated by a non-reverting mutation in a second gene.

25 8. A vaccine according to claim 7 wherein the second gene is an *aro* gene, a *pur* gene, the *htrA* gene, the *ompR* gene, the *galE* gene, the *cya* gene, the *crp* gene or the *phoP* gene.

Sub E4 1

9. A vaccine according to claim 8 wherein the *aro* gene is *aroA*, *aroC*, *aroD* or *aroE*.

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Sub A5
10. A vaccine according to any one of the preceding claims wherein the mutation in the gene encoding a protein which promotes folding of extracytoplasmic proteins and/or the mutation in the second gene is a defined mutation.

5 11. A vaccine according to any one of the preceding claims wherein the bacterium has no uncharacterised mutations in the genome thereof.

10 12. A vaccine according to any one of the preceding claims wherein the bacterium is a bacterium that infects via the oral route.

13. A vaccine according to any one of the preceding claims wherein the bacterium is from the genera *Salmonella*, *Escherichia*, *Vibrio*, *Haemophilus*, *Neisseria*, *Yersinia*, *Bordetella* or *Brucella*.

15 14. A vaccine according to claim 13 wherein the bacterium is *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella choleraesuis*, *Salmonella dublin*, *Escherichia coli*, *Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Yersinia enterocolitica*, *Bordetella pertussis* or *Brucella abortus*.

20 15. A vaccine according to any one of the preceding claims wherein the bacterium is genetically engineered to express an antigen from another organism.

25 16. A vaccine according to claim 15 wherein the antigen is fragment C of tetanus toxin.

17. A vaccine according to claim 15 or 16 wherein expression of the antigen is driven by the *nirB* promoter or the *ltrA* promoter.

30 18. A bacterium as defined in any one of the preceding claims for use in a method of vaccinating a human or animal.

19. Use of a bacterium as defined in any one of the preceding claims for the manufacture of a medicament for vaccinating a human or animal.

20. A method of raising an immune response in a host, which method comprises administering to the host a bacterium attenuated by a non-reverting mutation in a gene encoding a protein which promotes folding of extracytoplasmic proteins.

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